

The gut microbiota and childhood weight development

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VALORISATION

The purpose of research is obtaining results that can be put into use to help the society. This implies that the results of studies should have implications for policy and project implementation. In other words, this is known as valorisation, which can be fully defined as: “The process of value-creation out of knowledge, by making this knowledge suitable and available for economic or societal utilisation”.¹ The commercialisation of knowledge by generating patents and license contracts is an example of economic utilisation while societal utilisation involves making knowledge generated from research findings available to the population, policy makers and public organisations.

The studies presented in this thesis were aimed at: 1) examining associations between the gut microbiota composition and childhood (over)weight development; 2) examining the impact of childhood exposure to oral antibiotics on (over)weight development; and 3) addressing the methodological challenge of reducing high dimensional data of the gut microbiota in relation to latent BMI z-score trajectories. We showed that both the gut microbiota composition and early exposure to antibiotics were associated with childhood (over)weight development. However, due to their observational nature, studies in this thesis only yield associations and not causal relationships. Therefore, in this chapter, I will present some recommendations with regards to the findings obtained during my PhD project and how these findings can be applied to overcome this problem. This may aid in the prevention of overweight/obesity in children who are in the process of developing this and in the treatment of children already suffering from overweight/obesity.

A large percentage of the population is already aware of some of the factors that are known to be associated with obesity, but few individuals are aware of the millions of micro-organisms present in our gastrointestinal tract and their relation with health. Moreover, most results obtained from research are not accessible to the public but mostly found in databases that can only be obtained through subscription. In our study, the population of interest were children hence our targeted audience are parents, general practitioners, and especially paediatricians. In my opinion the first move will be to inform parents on the importance of the gut microbiota on childhood health, including its potential association with childhood obesity. Creating awareness of the importance of the gut microbiota in health will go a long way to help parents improve the lifestyle of their children.

We showed that early exposure to antibiotics was associated with childhood weight development. In addition, antibiotics have been reported to have a perturbative effect on the composition of the gut microbiota and lead to an increase of bacterial strains that are resistant to antibiotics. The major concern will be to minimise the prescription of antibiotics to children suffering from viral self-limiting respiratory tract infections. The Netherlands has been known internationally for its leading role in increasing awareness

about antibiotic use, by implementing restrictive antibiotic prescription guidelines. Meanwhile a lot still has to be done in other countries to achieve this aim e.g. southern European, Asian, and developing countries, and the United States of America.^{2,3} Therefore, strict guidelines for the prescription of antibiotics should be established and in countries with already established guidelines, adherence of GP's to the guidelines should be monitored for adequate antibiotic prescription. However, these guidelines are mainly based on antimicrobial susceptibility and resistance. In addition to existing cartoons to create awareness for antibiotic resistance (e.g. the Luke and Lucey cartoon “Auntie biotica”), cartoons demonstrating the negative impact of antibiotics that have direct impact on the patients such as the perturbation of the microbiota and associated effects on weight could be produced to help deliver the message to parents or the society.

To help prevent the overuse of antibiotics and their potential detrimental health effects, medical doctors should restrict the prescription of antibiotics according to the national guidelines. They should be able to educate their patients (especially parents) on the disadvantages of antibiotics and with the help of the public health sector, produce cards/flyers containing this information and share them. In this regards, this will help create awareness of antibiotics usage especially in children and will prevent them from unnecessary antibiotic usage.

For the treatment of childhood overweight/obesity, this will require further research to critically investigate if the associations seen in our and other studies are actually causal as most of the previous studies have been cross-sectional and causality cannot be established by such studies. Prospective studies or birth cohorts with multiple follow-up time-points from birth throughout infancy and childhood, and with faecal samples obtained at the same time of anthropometric outcomes will enable us to better monitor the composition of the microbiome and its association to weight development. This should also include an extensive documentation of lifestyle factors to better control for confounding factors. Some human intervention studies involving the transplantation of gut microbiota obtained from healthy donors to diseased recipients have already been carried out in adults.^{4,5} Such studies could be used to investigate if effects of the microbiota are causal in both adults and children. Future studies, could then implement the method of synthetic faecal transplantation^{6,7} to investigate the causal effect of the gut microbiota on childhood over (weight) development. Such studies should be extended to the different continents of the world by carrying out a high interrogation of the gut microbiota composition up to the species level to enable us to have a deeper insight into whether effects are similar in different geographic and ethnic populations. Also advanced statistical methodology for high dimensional data reduction and longitudinal data analysis applied to data with larger sample sizes are needed.

Above all, it is important to mention that this is still a very new area of research which so far has revealed new leads as to how the gut microbial composition relates to different aspects of human health especially childhood obesity. *Akkermansia* has consistently been reported in previous studies, as well as in our study, to be inversely associated with body weight in both mice⁸ and humans.^{9,10} We therefore recommend further studies (e.g. trials) to investigate the potential use of *Akkermansia* as a probiotic with a positive effect on weight management. Methanogenic archaea (specifically *M. smithii*) on the other hand have been found to be positively associated with body weight. It is thought that to achieve a reduction or elimination of *M. smithii* from the colon, bacteria such as sulphate reducing bacteria (SRB) could be incorporated into the colon to outcompete the methanogens for H₂. However, this should be preceded by experiments aiming at determining the conditions that would effectively reduce the methanogenic population.¹¹ Future animal studies, which involve the administration of only archaea or in combination with other microbes that compete with archaea for hydrogen are warranted.

Such studies might enable us to confirm causal relationships between *Akkermansia*, methanogenic archaea and weight development and provide new leads for intervention strategies such as the production of probiotics. Current evidence for probiotics in the prevention and treatment of most diseases is very limited. However, most probiotic strains and products were initially not specifically selected to treat or prevent a single disease. Therefore, if causality is finally established, these new candidates that appear to be specifically involved in weight development might appear to be more promising by administering the bacteria to overweight subjects through probiotics. From all previous studies conducted in this area of research including ours, there are strong indications that the gut microbiota remains a promising target in the fight for childhood (over) weight development. However, only when causality is established can we be very sure to start applying the findings obtained for treatment purposes.

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